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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
MCMILLIAN, KARA RENITA

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
07/29/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	09/980,039	DAVIS, BONNIE	
	Examiner	Art Unit	
	KARA R. MCMILLIAN	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-10 and 12-22* is/are pending in the application.

4a) Of the above claim(s) *4-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 12-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5-5-10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment/ Arguments

No amendments to the claims were made. Claims 4-10 were previously withdrawn. Claims 3, 11, 23 and 24 were previously canceled. Claims 1, 2 and 12-22 are presented for examination.

Applicant's arguments filed May 6, 2010 have been fully considered but they are not persuasive. Applicants argue that the Richardson et al. reference employed in the current rejection is cited in the original specification. Applicants further argue that this reference does not render their claims obvious.

This argument is found not persuasive because Applicant's arguments do not comply with 37 CFR 1.111(c) because they do not clearly point out the patentable novelty which he or she thinks the claims present in view of the state of the art disclosed by the references cited or the objections made. Further, they do not show how the amendments avoid such references or objections.

Applicants further argue that it was not clear to Richardson et al. that their in vitro findings in male tissue could be applied even to intact female animals, not to mention humans.

This argument is found not persuasive because Richardson et al. actually teach that LH-RH release by acetylcholine was blocked by a nicotinic blocker but not by atropine, a muscarinic blocker, and that said findings with atropine in vitro in male rats would not be expected to be predictive of in vivo findings in females. Thus Richardson

et al. teach that data with respect to atropine would not be predictive of in vivo findings in females however, Richardson et al. do not teach that other findings are not predictive of in vivo findings. Richardson et al. specifically teach that their direct studies of LH-RH release from hypothalami in short-term culture suggest that acetylcholine's progonadotrophic effects are indeed mediated at the hypothalamic level via stimulation of LH-RH secretion (page 2688). Furthermore, Richardson et al. teach that the anticholinesterase neostigmine potentiates the actions of acetylcholine by inhibiting cholinesterases that degrade acetylcholine and thus further stimulates LH-RH release (page 2688).

Applicants further argue that Richardson et al. teach an effect at 1 μM of neostigmine and Applicants provide an article by Ueki et al. which teach the IC_{50} of neostigmine for acetylcholinesterase inhibition in the rat is 0.11 μM. Thus applicants argue that acetylcholinesterase would have been overwhelmingly inhibited by 1 μM neostigmine and it would have been doubtful that such a dose could be administered to living animals.

This argument is found not persuasive because Applicants do not claim any specific amounts for acetylcholinesterase inhibitors. Based on the recited teachings, an ordinary skilled artisan would use the concentrations as taught in Davis et al. which inhibits acetylcholinesterase in humans and thus increases levels of acetylcholine resulting in LH-RH release. Based on the teachings of Richardson et al. in rats, there is a reasonable expectation that administration of acetylcholinesterase inhibitors would

increase acetylcholine levels and thus stimulate ovulation in humans since animal studies in rats are typically predictive of in vivo effects in humans.

Applicants further argue that the instant application provides information, although not referenced that cholinergic agents could be given to living animals in doses capable of releasing LH by stating that in intact rats, injection of acetylcholine into the lateral ventricle stimulates LH release and that this can be blocked with atropine or enhanced with prostigmine.

This argument is found not persuasive because just as Richardson et al., Applicants data (although not shown) is represented in rats. Thus it is obvious based on Applicants own statements that data obtained in rats are predictive of in vivo effects in humans.

Applicants further argue that the data most directly indicating cholinergic stimulation of the hypothalamic-pituitary-reproductive axis were obtained in beagle dogs and submitted to the patent office in the response of December 1, 2008.

These data are found not persuasive because it is not clear that the Applicants were in possession of said data at the time the instant invention was made as Applicants have not submitted said data in the form of a declaration. Furthermore, the data referenced is not considered unexpected since based on the combined teachings, it would be obvious that galanthamine would stimulate ovulation since galanthamine is an acetylcholinesterase inhibitor which results in increases in acetylcholine levels that cause release of LH-RH resulting in ovulation.

Thus for the reasons of record and for the reasons presented above, the previous rejections under 35 USC 103 are hereby maintained and reproduced below. This action is made FINAL.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2 and 12-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Richardson et al. (1982, PNAS, Volume 79, pages 2686-2689) in view of Amoss et al. U.S. Patent No. 4,072,668 and Davis et al. U.S. Patent No. 6,150,354.

Claims 1-2 and 12-21 of the instant application claim a method of treating the failure of ovulation in a human patient by stimulation of the hypothalamic-pituitary-gonadal axis comprising the administration of an acetylcholinesterase inhibitor at the beginning of the follicular phase such as galanthamine or analogs of galanthamine which have a central effect and thereafter determining whether a normal follicular response has been obtained and deciding further administration of the compound based on the results.

Richardson et al. teach that the control of hypothalamic luteinizing hormone-releasing hormone secretion is complex, however it is well known that neuromodulators

and neurotransmitters play a major role in the regulatory process (see page 2686). Richardson et al. teach that acetylcholine as well as its degradative enzymes are present in the hypothalamus, suggesting physiological roles at this site (see page 2686). Richardson et al. further teach that atropine, an anticholinergic, when administered systemically in large doses, abolishes ovulation in rats (see page 2686). Richardson et al. further teach that acetylcholine stimulates gonadotropin release in vivo and in vitro through mechanisms dependent on the hypothalamus suggesting that a hypothalamic site as the locus of action of acetylcholine's stimulatory pro-gonadotropic effects (see page 2686).

The study of Richardson et al. examined the release of luteinizing hormone-releasing hormone (LHRH) from rat medial basal hypothalamus (see abstract). Richardson et al. teach that acetylcholine and neostigmine which potentiates acetylcholine by inhibiting cholinesterase activity, markedly stimulated LHRH release (see abstract, pages 2686 and 2687 and Figure 3 on page 2688). Although Richardson et al. do not specifically teach that acetylcholine stimulates LHRH release in humans, it would be obvious to a person of ordinary skill in the art that the experiments of Richardson et al. would apply to humans since experiments are routinely performed in animal models that predict what would occurs in humans.

Richardson et al. do not specifically teach treating failure of ovulation. Richardson et al. do not teach administering the compounds at the beginning of the follicular phase. Richardson et al. do not teach the administration of acetylcholinesterase inhibitors claimed in instant claim 1.

Amoss et al. teach in column 1 lines 14-45 that the pituitary gland is attached by a stalk to the region in the base of the brain known as the hypothalamus and the pituitary gland has two lobes, the anterior and the posterior lobes. The anterior lobe of the pituitary gland secretes a number of hormones which in turn stimulate the secretion into the bloodstream of other hormones from the peripheral organs, in particular, follicle stimulating hormone and luteinizing hormone are released by the pituitary gland. The release of a hormone by the anterior lobe of the pituitary gland usually requires a prior release of another class of hormones produced by the hypothalamus. The hypothalamic hormone which acts as a releasing factor for luteinizing hormone (LH) from the pituitary is luteinizing hormone releasing factor (LRF).

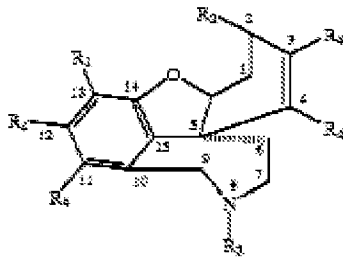
Amoss et al. further teach that it has been demonstrated that female mammalians who have no ovulatory cycle and who show no pituitary or ovarian defect begin to secrete normal amounts of the gonadotropins, LH and follicle stimulating hormone (FSH) after the administration of LRF and the administration of LRF is suitable for the treatment of those cases of infertility where the functional defect resides in the hypothalamus (see column 1 lines 46-53). Amoss et al. further teach that ovulation can be induced in female mammalians by the administration of LRF (see column 1 lines 53-54).

Richardson et al. teach that acetylcholine and neostigmine which potentiates acetylcholine by inhibiting cholinesterase activity, markedly stimulates LHRH also known as LRF release. Amoss et al. teach that release of LRF (LHRH) from the hypothalamus induces the release of LH and FSH from the pituitary and thus results in

the induction of ovulation. Accordingly, it would be obvious to a person of ordinary skill in the art at the time of the instant invention that the administration of acetylcholine or an acetylcholinesterase inhibitor which potentiates acetylcholine would result in the release of LHRF (LRF) from the hypothalamus leading to the release of LH and FSH from the pituitary gland resulting in the induction of ovulation. Thus an ordinary skilled artisan would be motivated to administer acetylcholine or an acetylcholinesterase inhibitor to increase levels of acetylcholine in the brain in order to stimulate release of LHRH (LRF) from the hypothalamus with a reasonable expectation of treating failure of ovulation.

Furthermore, Amoss et al. teach that LH and FSH in combination regulate the functioning of the gonads to produce progesterone and estrogen in the ovaries as well as regulate the production and maturation of gametes (see column 1 lines 25-33). Thus it would be obvious to a person of ordinary skill in the art to administer the compounds at the beginning of the follicular phase since the compounds would cause the release of LH and FSH which contribute to the maturation of ovaries and induce ovulation (the expulsion of a mature ovary).

Davis et al. teach analogs of galanthamine, particularly those wherein the methoxy and hydroxy groups are replaced by, for example carbamate groups, or the methoxy group is replaced by hydroxy (see abstract). Claim 2 of Davis et al. claims a method of inhibiting acetylcholinesterase activity comprising administering a compound of the following formula:



wherein R1 or R2 may be a hydrogen; hydroxyl; alkoxy of 1-6 carbon atoms; monoalkyl or dialkyl or aryl carbamate; etc. It is also noted that galanthamine, and specific alkyl carbamates are taught as acetylcholinesterase inhibitors (see column 29, line 35 to column 30, line 60). Davies et al. also teach that the compounds pass the blood brain barrier easily and distribute themselves between the central and peripheral nervous systems in such a way that their effects are mainly central (see column 7 lines 50-54). Davis et al. also teach that it is possible to increase acetylcholine levels by decreasing the amount or activity of the acetylcholinesterase (see column 7, lines 44-48). Thus Davies et al. teach that the administration of the centrally-acting galanthamine analogs which inhibit acetylcholinesterase, increase levels of acetylcholine through its inhibition of acetylcholinesterase.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to administer an acetylcholinesterase inhibitor of Davis et al. in order to induce ovulation because (1) Davis et al. teach that the inhibition of acetylcholinesterase causes an increase in acetylcholine; (2) Richardson et al. teach that acetylcholine and compounds which potentiate acetylcholine through inhibition cholinesterase activity, markedly stimulate LHRH also known as LRF release; and (3)

Amoss et al. teach that release of LRF (LHRH) from the hypothalamus induces the release of LH and FSH from the pituitary resulting in the induction of ovulation. One would have been motivated to administer the acetylcholinesterase inhibitors of Davis et al. because of an expectation of success in inducing ovulation.

It is noted that the claimed recitation of a duration of action of from 1 to 100 hours is a property of the acetylcholinesterase inhibitor to be administered. Since the same compounds are cited herein as obvious, the limitation is met. A compound and its properties are inseparable. *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963).

Furthermore, it is obvious to an ordinary skilled artisan to administer a drug and determine if the desired response is achieved. It is also obvious to an ordinary skilled artisan to determine if a condition has been treated or if further treatment is necessary. Said limitations as claimed in claim 1 of the instant application are routinely performed and not considered inventive. Thus said limitations are also rendered obvious.

Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Richardson et al. (1982, PNAS, Volume 79, pages 2686-2689) in view of Amoss et al. U.S. Patent No. 4,072,668 and Davis et al. U.S. Patent No. 6,150,354 as applied to claims 1-2 and 12-21 above and further in view of Polinsky (1998, Clinical Therapeutics, Volume 20, No. 4, pages 634-647).

Claim 22 of the instant application claim a method of treating the failure of ovulation in a human patient comprising the administration of an acetylcholinesterase inhibitor such as rivastigmine which have a central effect and thereafter determining

whether a normal follicular response has been obtained and deciding further administration of the compound based on the results.

Richardson et al. in view of Amoss et al. and Davis et al. is as set forth above. Said references do not teach the acetylcholinesterase inhibitor rivastigmine.

Polinsky teaches that rivastigmine is an acetylcholinesterase inhibitor with brain-region selectivity and a long duration of action (see abstract). Polinsky further teaches that rivastigmine inhibits acetylcholinesterase mainly in the central nervous system with some inhibition in the peripheral (see abstract and page 639).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to administer the acetylcholinesterase inhibitor, rivastigmine as taught by Polinsky in order to induce ovulation because (1) Davis et al. teach that the inhibition of acetylcholinesterase causes an increase in acetylcholine; (2) Richardson et al. teach that acetylcholine and compounds which potentiate acetylcholine through inhibition of cholinesterase activity, markedly stimulate LHRH also known as LRF release; and (3) Amoss et al. teach that release of LRF (LHRH) from the hypothalamus induces the release of LH and FSH from the pituitary resulting in the induction of ovulation. One would have been motivated to administer rivastigmine because of an expectation of success in inducing ovulation. Thus claim 22 is rendered obvious.

Conclusions

Claims 1, 2 and 12-22 are rejected. Claims 4-10 are withdrawn. Claims 3, 11, 23 and 24 are canceled. No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KARA R. MCMILLIAN whose telephone number is (571)270-5236. The examiner can normally be reached on Monday-Thursday from 8:30 am- 6:00 pm and every other Friday from 8:30 am- 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kara R. McMillian/
Examiner, Art Unit 1627

KRM

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1627